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08/908,884

08/08/1997

XINNIAN DONG

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05/26/2005

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER

KUBELIK, ANNE R

ART UNIT

PAPER NUMBER

1638

DATE MAILED: 05/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/908,884

Applicant(s)

DONG ET AL.

Examiner

Anne R. Kubelik

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 March 2005.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-13,15-29,36,40-42 and 47-54 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-13,15-29,36,40-42 and 47-54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 April 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-2, 4-13, 15-29, 36, 40-42 and 47-54 are pending.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

3. Claims 36 and 49 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility. The rejection is repeated for the reasons of record as set forth in the Office action mailed 31 August 2004. Applicant's arguments filed 3 March 2005 have been fully considered but they are not persuasive.

Applicant urges that it is credible that using an antibody will identify expression patterns of plants that are susceptible to pathogenic infection. Applicant that further discusses Office policy on rejections over whether an invention is credible (response pg 10-12).

This is not found persuasive. First, the rejection is not that the claimed invention is not supported by a credible utility, but is instead that the claimed invention is not supported by either a substantial asserted utility or a well-established utility. An invention may pass the credibility prong of the utility rejection, but fail the substantial asserted utility or a well-established utility prongs. The invention cannot have a well-established utility because no other NPR1 genes/proteins have ever been isolated. The invention does not have a substantial utility because the utility of monitoring the level of the protein in a plant because no substantial utility is given for this information. Furthermore, even the utility asserted in the response, identification of

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expression patterns of plants that are susceptible to pathogenic infection, is not substantial because further research is required to determine the “real world” context of use. Applicant does not teach how to use the invention to identify plants that are susceptible to pathogenic infection - further research is required to identify the pattern of expression associated with susceptibility - and the specification does not teach what one would do with that information. Thus, a method of making the protein has no substantial or well-established utility.

Applicant urges that the protein can be used to generate diagnostic anti-NPR antibodies, and the protein itself can also be used for the isolation and purification of NPR-binding proteins (response pg 12).

This is not found persuasive. The specification does not teach how to use diagnostic anti-NPR antibodies as further research is required to identify the pattern of expression associated with susceptibility, and the specification does not teach what one would do with that information. Any protein can also be used for the isolation and purification of proteins that bind to it. Further research is required to identify those proteins and to find a utility for them. The method of making the protein has no substantial or well-established utility.

Claim Rejections - 35 USC § 112

4. Claims 36 and 49 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The rejection is repeated for the reasons of record as set forth

in the Office action mailed 31 August 2004. Applicant's arguments filed 3 March 2005 have been fully considered but they are not persuasive.

Applicant urges that for the reasons above the rejection should be withdrawn (response pg). This is not found persuasive for the reasons indicated above.

5. Claims 47-52 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 31 August 2004. Applicant's arguments filed 3 March 2005 have been fully considered but they are not persuasive.

Applicant urges that support is found on pg 41-44 (response pg 13).

This is not found persuasive. Those pages teach the following: pg 41, restriction mapping of a 7.5 kb region that complements three *npr1* mutants; pg 41-42, Northern analysis of NPR1; pg 42, sequencing of NPR1; pg 43, isolation of NPR1 clones; pg 44, identification of ankyrin repeats in NPR1 and transformation of plants with SEQ ID NO:2. There is no support for claiming nucleic acids encoding an acquired resistance polypeptide comprising an ankyrin repeat complementing any acquired resistance mutant.

6. Claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52 remain rejected and claims 53-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The

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rejection is repeated for the reasons of record as set forth in the Office action mailed 31 August 2004, as applied to claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52. Applicant's arguments filed 3 March 2005 have been fully considered but they are not persuasive.

Applicant urges that one of skill in the art would appreciate that an essential feature of the claimed invention is the ability of the claimed nucleic acid to encode proteins that confer disease resistance on plants; all the claims have that functional limitation, and assays are described so that one of skill in the art could determine whether a protein has that function (response pg 13-14).

This is not found persuasive because Applicant has not made the necessary and sufficient correlation between structure and function.

Applicant urges that further characterization of claimed molecules beyond the ankyrin repeat is not necessary to distinguish the claimed proteins from other proteins (response pg 14).

This is not found persuasive. Ankyrin repeats comprise less than 10% of the total length of the proteins encoded by the claimed nucleic acids and those ankyrin repeats are present in a great number of other proteins that did not have AR activity. Sedgwick et al (1999, Trends Biochem. Sci. 24:311-316) teach the ankyrin repeats are found in a wide range of proteins, including inhibitors, developmental regulators, cytoskeleton organizers and toxins and that in most of these proteins ankyrin repeats are combined with unrelated structural modules (pg 311, column 3, paragraph 1). Ankyrin repeats appear to be involved in protein-protein interactions and not in the unique role of the protein (Sedgwick et al, paragraph spanning pg 311-312, and Cao et al, 1997, Cell 88:57-63, pg 61, left column, paragraph 3¹).

¹ The first author of this paper is one of the instant inventors, Hui Cao.

Furthermore, the function of NPR1 requires more than the ankyrin repeats. Kinkema et al (2000, Plant Cell 12:2339-2350)² teach that nuclear localization is required for activation of PR gene expression by NPR1; mutation in the nuclear localization signals located at the C-terminal end of NPR1 prevents its nuclear location and thus, activation of PR-1 expression (Fig. 3B, pg 2344, right column, paragraph 2, to pg 2345, right column, paragraph 1). Ryals et al (1997, Plant Cell 9:425-439) teach that Arg⁴³² is critical for function (Table 3). Aravind et al (1999, J. Mol. Biol. 285:1353-1361) teach that NPR1 has a POZ domain, which is involved in protein-protein interaction, spanning amino acids 62-176 (Fig. 1); Fan et al (2002, Biology of Plant-Microbe Interactions 3:94-98)³ demonstrated its importance in induction of PR gene expression (paragraph spanning pg 95-96). Thus, a description of a nucleic acid encoding an NPR1 protein must include at least these structural features. Applicant urges that the structural characteristics are that they hybridize to or encode proteins with 80% identity to one of the disclosed nucleic acids (response pg 14-15).

This is not found persuasive. First, not all claims require that the nucleic acids hybridize to or encode proteins with 80% identity to one of the disclosed nucleic acids. Second, because the specification does not describe all the necessary and sufficient structural motifs that distinguish nucleic acids that encode ankyrin-repeat containing proteins that do confer disease resistance upon a plant from nucleic acids that encode ankyrin-repeat containing proteins that do not confer disease resistance upon a plant or that distinguish nucleic acids that hybridize to or encode proteins with 80% identity to one of the disclosed nucleic acids and that encode ankyrin-repeat containing proteins that do confer disease resistance upon a plant from nucleic acids that

² One of the authors of this paper is one of the instant inventors, Xinnian Dong.

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hybridize to or encode proteins with 80% identity to one of the disclosed nucleic acids and that encode ankyrin-repeat containing proteins that do not confer disease resistance.

Furthermore, claim 6 is drawn to such a nucleic acid from any Cruciferae; Cruciferae comprises at least 162 genera and the genus *Arabidopsis* alone comprises at least 53 species. The specification describes only one NPR1 gene (SEQ ID NO:1) from only one of these species, *Arabidopsis thaliana*.

Claim 5 is drawn to such a nucleic acid from any *Solanaceae*. *Solanaceae* comprises at least 57 genera; the genus *Nicotiana* alone comprises at least 72 species. The specification describes only one possible NPR1 gene (SEQ ID NO:13) from only one of these species, *Nicotiana glutinosa*.

7. Claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52 remain rejected and claims 53-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for NPR1 coding sequences from *Arabidopsis* that comprise SEQ ID NOs:1 and 2, does not reasonably provide enablement for any nucleic acid that encodes an ankyrin-repeat-containing disease resistance protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 31 August 2004, as applied to claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52. Applicant's arguments filed 3 March 2005 have been fully considered but they are not persuasive.

³ One of the authors of this paper is one of the instant inventors, Xinnian Dong.

Applicant urges that screening molecules falling within their claims is a routine step in the process of isolating molecules with the desired characteristics and is thus not undue experimentation (response pg 16).

This is not found persuasive. The specification does not teach where to find nucleic acid within the scope of the claims, especially nucleic acids encoding proteins with at least 80% identity to SEQ ID NO: 3 or 14, and does not teach how to make the nucleic acids. Thus, undue trial and error would be required to make the claimed nucleic acids.

Applicant urges that sequencing and comparing the sequence to a reference sequence has become automated in recent years (response pg 16-17).

This is not found persuasive. "Recent years" is not the standard; what was routine at the time of filing is. Furthermore, more than sequencing and comparing the sequence to a reference sequence is required. The specification does not teach how to make or where to find the claimed nucleic acids. Given this lack of guidance, undue trial and error experimentation would be required to make the claimed nucleic acids.

Applicant urges that new claims 53-54 require that the protein encoded by the nucleic acid has an amino acid sequence with at least 80% identity to SEQ ID NO: 3 or 14; the application enables these as standard methods can be used to compare sequences (response pg 17).

This is not found persuasive. Given the claim breadth, unpredictability, and lack of guidance, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding proteins with 80% identity to SEQ ID NO:3 or 14. Making all possible single amino acid substitutions in an 593 amino acid long protein like that encoded by SEQ ID NO:2 would require making and analyzing 19^{593} nucleic acids; these proteins would

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have 99.8% identity to SEQ ID NO:3. Making all possible single amino acid substitutions in an 588 amino acid long protein like that encoded by SEQ ID NO:13 would require making and analyzing 19^{588} nucleic acids; these proteins would have 99.8% identity to SEQ ID NO:14. Because nucleic acids encoding proteins with 80% identity to SEQ ID NO:3 would encode proteins with 118 amino acid substitutions and nucleic acids encoding proteins with 80% identity to SEQ ID NO: would encode proteins with 117 amino acid substitutions, many more than 19^{593} or 19^{588} nucleic acids would need to be made and analyzed. Thus, making and analyzing proteins with 117 or 118 amino acid substitutions that also have disease resistance activity would require undue experimentation.

Applicant urges that one of skill in the art could determine the sequence of NPR genes from other plants and compare them to the Arabidopsis sequences in the specification to look for ankyrin repeats and test for expression for disease resistance (response pg 18).

This is not found persuasive. As discussed in the previous Office action, the presence of an ankyrin repeat does not mean a protein plays a role in plant disease resistance. Sedgwick et al (1999, Trends Biochem. Sci. 24:31 1-316) teach the ankyrin repeats are found in a wide range of proteins, including inhibitors, developmental regulators, cytoskeleton organizers, and toxins and that in most of these proteins, ankyrin repeats are combined with unrelated structural modules (pg 31 1, column 3, paragraph 1). Ankyrin repeats appear to be involved in protein-protein interactions and not in the unique role of the protein (Sedgwick et al, paragraph spanning pg 311-312, and Cao et al, 1997, Cell 88:57-63, pg 61, left column, paragraph 3⁴).

⁴ The first author of this paper is one of the instant inventors, Hui Cao.

The function of NPR1 requires more than the ankyrin repeats. The specification teaches that NPR1 is localized to the nucleus (pg 46-47). Kinkema et al (2000, Plant Cell 12:2339-2350)⁵ teach that nuclear localization is required for activation of PR gene expression by NPR1; mutation in the nuclear localization signals located at the C-terminal end of NPR1 prevents its nuclear location and thus, activation of PR-1 expression (Fig. 3B, pg 2344, right column, paragraph 2, to pg 2345, right column, paragraph 1). The claims are not directed to proteins with these motifs.

Additionally, other amino acids are critical for NPR1 function. Ryals et al (1997, Plant Cell 9:425-439) teach that Arg⁴³² is critical for function (Table 3). The specification does not teach the requirement for this amino acid.

Aravind et al (1999, J. Mol. Biol. 285:1353-1361) teach that NPR1 has a POZ domain, which is involved in protein-protein interaction, spanning amino acids 62-176 (Fig. 1); Fan et al (2002, Biology of Plant-Microbe Interactions 3:94-98)³⁹⁶ demonstrated its importance in induction of PR gene expression (paragraph spanning pg 95-96). The specification does not teach this domain and the claims are not directed to a nucleic acid encoding a protein with this domain.

Thus, the specification does not teach all the necessary and sufficient structural motifs that would enable one to distinguish nucleic acids that encode ankyrin-repeat containing proteins that do confer disease resistance upon a plant from nucleic acids that encode ankyrin-repeat containing proteins that do not confer disease resistance upon a plant.

⁵ One of the authors of this paper is one of the instant inventors, Xinnian Dong.

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See *Plant Genetic Systems N.V. v. DeKalb Genetics Corp.*, 65 USPQ2d 1452 (CA FC 2003), which states that a “[p]atent claiming [a] ‘pioneering’ invention is not entitled to lowered standard for meeting enablement requirement of 35 U.S.C. §112.”

Applicant urges that isolation of genes from different organisms is standard, especially if a corresponding gene is available from other organisms; sequence and sequence comparison and assaying are also routine (response pg 18-19).

This is not found persuasive because the specification does not teach how to make or where to find the claimed nucleic acids. Given this lack of guidance, undue trial and error experimentation would be required to make the claimed nucleic acids.

Additionally, the specification does not teach any nucleic acid, other than SEQ ID NOs:1 and 2, that are able to complement any acquired resistance mutant, including any *Arabidopsis npr* mutant. Even SEQ ID NO:13 has not been shown to complement any of these mutants, and it is not clear that it would be able to do so.

The specification fails to provide evidence that the *N. glutinosa* nucleic acid SEQ ID NO:13 encodes a protein that confers disease resistance to a plant expressing the protein and has a functional relatedness to the *Arabidopsis* NPR1 gene.

8. Claims 10-13, 15-29, 36, 40-42 and 47-52 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is repeated for the reasons of record as set forth in the Office action mailed 31

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August 2004. Applicant's arguments filed 3 March 2005 have been fully considered but they are not persuasive.

Claims 10-12, 17, 22, 36 and 40 are indefinite in their recitation of "hybridizes". The hybridization conditions are not defined; thus it is unclear which nucleic acids fall within the claims.

Applicant urges that the examples on pg 12, 49 and 51 of the specification make the meaning of this term definite (response pg 19-20).

This is not found persuasive because examples do not define a term. If those conditions are what applicant wishes "hybridizes" to mean, they should be recited within the claim.

Claim Rejections - 35 USC § 102

9. Claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52 remain rejected and claims 53-54 are rejected under 35 U.S.C. 102(e) as being anticipated by Ryals et al (US Patent 6,091,004, filed June, 1996). The rejection is repeated for the reasons of record as set forth in the Office action mailed 31 August 2004, as applied to claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52. Applicant's arguments filed 3 March 2005 have been fully considered but they are not persuasive.

Applicant urges that they believe they are the first to invent the claimed subject matter and that an interference should be declared (response pg 19).

This is not found persuasive. An interference cannot be declared until all other issues in the case are resolved. Additionally, Applicant must request an interference under 37 CFR 1.607 and make a showing under 37 CFR 1.608(a). See MPEP 2307 and 2308.

Applicant urges that if at least one of the pending claims is found allowable and claiming the same invention as '004, the interference be declared (response pg 20).

This is not found persuasive. No claims are allowable.

10. Claims 1-2, 4, 6-13, 15-25, 28-29, 36 and 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (1992, Plant Cell 4:1575-1588) in light of Applicant's response filed 18 May 2004. The rejection is repeated for the reasons of record as set forth in the Office action mailed 31 August 2004. Applicant's arguments filed 3 March 2005 have been fully considered but they are not persuasive.

Applicant urges that Zhang et al fails to disclose the peptide as triggering a plant acquired resistance response (response pg 21).

This is not found persuasive because the rejection is made on the basis of Applicant's assertion filed 18 May 2004 states "disruption of the ankyrin consensus ... rendered plants susceptible to disease; evidencing the ankyrin motif ... as structurally and functionally defining", *i.e.*, that a ankyrin motif defines a protein as an acquired resistance polypeptide. Applicant's arguments filed 3 March 2005 urge that further characterization of claimed molecules beyond the ankyrin repeat is not necessary to distinguish the claimed proteins from other proteins (response pg 14). As the protein has an ankyrin repeat, it would inherently trigger a plant acquired resistance response

Double Patenting

11. Claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52 remain provisionally rejected and claims 53-54 are provisionally rejected under the judicially created doctrine of double patenting over

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claims 1-25 of copending Application No. 09/908,323. The rejection is repeated for the reasons of record as set forth in the Office action mailed 31 August 2004, as applied to claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52. Applicant's arguments filed 3 March 2005 have been fully considered but they are not persuasive.

Applicant urges that a terminal disclaimer will be filed when allowable subject matter is determined (response pg 27). This is acknowledged.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the

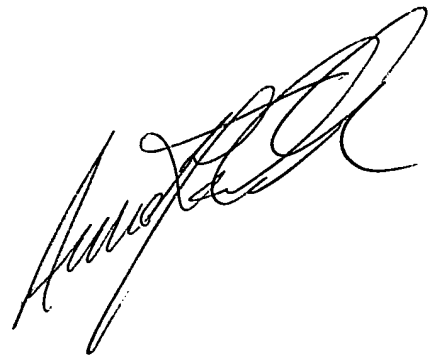
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problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Anne R. Kubelik, Ph.D.

May 23, 2005

A handwritten signature in black ink, appearing to read "Anne R. Kubelik", is located in the lower right quadrant of the page. The signature is stylized with a large, sweeping loop at the end.